Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Protocol)

Punja S, Shamseer L, Hartling L, Urichuk L, Vandermeer B, Nikles CJ, Vohra S

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane protocol, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 7

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents

Salima Punja[1], Larissa Shamseer[2], Lisa Hartling[3], Liana Urichuk[4,5], Ben Vandermeer[3], Catherine J Nikles[6], Sunita Vohra[3]

[1]Department of Medicine, University of Alberta, Edmonton, Canada. [2]Ottawa Methods Centre, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Canada. [3]Department of Pediatrics, University of Alberta, Edmonton, Canada. [4]Department of Psychiatry, University of Alberta, Edmonton, Canada. [5]Information & Evaluation Services, Addiction and Mental Health, Alberta Health Services, Edmonton, Canada. [6]Department of Medicine, The University of Queensland, Ipswich, Australia

Contact address: Sunita Vohra, Department of Pediatrics, University of Alberta, Aberhart Centre One, Room 9424, 11402 University Avenue, Edmonton, Alberta, T6G 2J3, Canada. svohra@ualberta.ca.

Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group.
Publication status and date: New, published in Issue 7, 2012.

Citation: Punja S, Shamseer L, Hartling L, Urichuk L, Vandermeer B, Nikles CJ, Vohra S. Amphetamines for attention deficit hyperactivity disorder (ADHD) in children and adolescents. *Cochrane Database of Systematic Reviews* 2012, Issue 7. Art. No.: CD009996. DOI: 10.1002/14651858.CD009996.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy and safety of amphetamines for ADHD in children and adolescents.

BACKGROUND

Description of the condition

Attention deficit hyperactivity disorder (ADHD) is among the most common pediatric psychiatric conditions, affecting around 5% of children worldwide (Polzancky 2007). ADHD is characterized by three core symptoms: inattention, impulsivity, and hyperactivity, which are more frequently displayed than would be typical in children of the same age (APA 2000). The core symptoms are often presented to various degrees in different children, breaking ADHD down into three subtypes: the predominantly inattentive type, the predominantly hyperactive-impulsive type, and the combined type (i.e. children displaying both inattention and hyperactivity) (APA 2000). The condition is often diagnosed through a rigorous set of criteria at a young age, usually between the ages of three and six (NIMH 2009). The potential for comorbidities is extremely high in this population and they are present in almost two-thirds of pediatric ADHD cases, with the most common being oppositional defiant disorder (ODD) (50%), conduct disorder (CD) (35%), anxiety disorder (33%), and depression (33%) (AHRQ 1999; Mayes 2009).

The symptoms of ADHD have been shown to permeate a child's performance across multiple settings, having long-term effects on their academic performance and social development. Studies have also shown that children with ADHD are more likely to be more irritable, impatient, and aggressive (NIH 2000). In addition, families who have children with ADHD often experience higher levels of parental stress and frustration, marital disruption, and social isolation (Edwards 1995). It has been estimated that 50% of childhood ADHD cases will persist into adolescence and adulthood (Biederman 1993), making it a chronic lifetime condition

for many.

Description of the intervention

A wide variety of treatments have been used for the management of ADHD including psychosocial interventions, dietary management, herbal and homeopathic remedies, and biofeedback; however, for the past few decades, stimulant medication has been the first line of treatment (APA 2000) and has been found to be effective in 70% to 90% of school-aged children (Wigal 1999; NIH 2000). Amphetamines are the second most frequently prescribed psychostimulants for pediatric ADHD, and are becoming an increasingly popular alternative for children who fail to respond to methylphenidate (Buck 2002). There are currently four different amphetamine preparations available. These include racemic amphetamine sulfate, dexamphetamine (dextroamphetamine or d-amphetamine sulfate), lisdexamphetamine, and a newer amphetamine mixture that contains four different amphetamine salts (Buck 2002).

How the intervention might work

Evidence has suggested that ADHD may be the result of insufficient production of norepinephrine and dopamine in the prefrontal cortex (Arnsten 2006). As such, the executive functions carried out by the prefrontal cortex are impaired, resulting in forgetfulness, distractibility, impulsivity, and inappropriate social behaviors (Anderson 1999). Others believe that the limbic system plays a major role in the pathophysiology of ADHD, and it is thought that hyperactivity and impulsivity result from abnormally low tonic dopamine activity within this region of the brain (Moore 2011). In either case, as a psychostimulant, amphetamines are thought to disrupt normal reuptake of neurotransmitters thereby increasing levels of norepinephrine and dopamine in these regions of the brain and resulting in restored executive functioning (Arnsten 2006). A Cochrane review of amphetamines for ADHD in adults found they improved short-term symptom severity (Castells 2011).

Why it is important to do this review

Despite being one of the most thoroughly researched disorders in medicine, one of the major controversies regarding ADHD is the use of psychostimulants as a treatment option. While current evidence suggests that amphetamines may be beneficial for improving the core symptoms of ADHD, its effects on academic and social domains remain inconsistent and unclear (NIH 2000). Wide variations in the use and prescription of amphetamines across communities suggests that there is a lack of consensus among practitioners regarding which people with ADHD should be treated with amphetamines. In spite of the wide use of amphetamines as a first or second line of therapy for pediatric ADHD, a systematic review assessing their efficacy and safety in this population has never been conducted. As primary stakeholders, it is imperative for healthcare providers, parents, and those diagnosed with ADHD to be aware of the most suitable treatment options available, and how they differ in terms of their efficacy and safety profiles. Our synthesis of all available randomized controlled trials on the efficacy and safety of amphetamines for pediatric ADHD will provide evidence to better inform clinical practice and further research planning of ADHD management.

OBJECTIVES

To assess the efficacy and safety of amphetamines for ADHD in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

Parallel and cross-over randomized controlled trials (RCTs).

Types of participants

Children and adolescents (less than 18 years of age) with a clinical diagnosis of ADHD according to specified diagnostic criteria, such as the DSM-III (APA 1987), DSM-IV (APA 2000), or equivalent. We will include trials that involve participants with some comorbid conditions (oppositional defiant disorder (ODD), conduct disorder (CD), anxiety, depression, learning disability). We will exclude trials that include participants with neuropsychological comorbidities, which require highly specialized treatment programs (for example, autism, bipolar disorder, psychosis).

Types of interventions

Intervention: any oral form of amphetamine (i.e. amphetamine, dexamphetamine, lisdexamphetamine, and mixed amphetamine salts (Adderall)), at any dose.
Control: placebo.

Types of outcome measures

Primary outcomes

1. Change in core ADHD symptoms (inattention, hyperactivity, impulsivity), as measured by a validated scale rated by children, parents, teachers, clinicians, or assessors such as the revised Conners' Parent Rating Scale (CPRS-R) (Conners 1998), the revised Conners' Teacher Rating scale (CTRS-R) (Conners 1998a), or the ADHD Rating Scale (Zhang 2005)*

Change scores and endpoint scores will be collected; however, priority will be given to change scores when both types of scores are available in the same study.

Secondary outcomes

1. Clinical improvement measured the by Clinical Global Impression-Improvement (CGI-I) scale*
2. School or academic performance as measured by school test results or by a validated scale*
3. Parental stress measured by a validated scale (for example, Parenting Stress Index (PSI) (Abidin 1997))*
4. Quality of life measured by a validated scaled (for example, Pediatric Quality of Life Inventory-32 (PedsQL-32) (Varni 1998))*
5. Retention: proportion of randomized participants who completed the trial

Adverse events

1. Proportion of adverse events*
2. Proportion of participants who experienced at least one adverse event as reported in the trials
3. Proportion of participants that drop out due to any adverse event

Outcomes marked with an * will be used to populate a 'Summary of findings' table.

Search methods for identification of studies

We will attempt to identify all relevant published and unpublished RCTs, irrespective of language, using the terms: Attention Deficit with Hyperactivity Disorder AND (child OR adolescent OR paediatric) AND (amphetamines OR dexamphetamine OR lisdexamphetamine OR mixed amphetamine salts).

Electronic searches

We will search the following electronic databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL)
2. MEDLINE
3. Medline In-Process & Other Non-Indexed Citations
4. EMBASE
5. PsycINFO
6. ProQuest Dissertations and Theses
7. metaRegister of Controlled Trials (*m*RCT)
8. The NHS National Research Register Archive
9. ClinicalTrials.gov
10. Networked Digital Library of Theses and Dissertations (NTLTD)

The complete search strategy for MEDLINE is below and will be modified as appropriate for the other databases.

1. exp Amphetamines/
2. (amphetamine$ or dexamphetamine$ or methamphetamine$ or dextroamphetamine$ or lisdexamphetamine$ or vyvanase$ or Dexedrin3 or desoxyn$ or adderall$).mp.
3. Central Nervous System Stimulants/
4. 1 or 2 or 3
5. exp Attention Deficit Disorder with Hyperactivity/
6. Child Behavior Disorders/
7. adhd.tw.
8. addh.tw.
9. adhs.tw
10. adhs.tw.
11. "ad/hd".tw.
12. hyperactiv$.tw.
13. hyper-activ$.tw.
14. overactiv$.tw.
15. over-activ$.tw.
16. hyperkinesis/
17. hyperkin$.tw.
18. hyper-kin$.tw.
19. hkd.tw.
20. (minimal adj3 brain$ adj3 (damag$ or disorder$ or dysfunc$)).tw.
21. (attention$ adj3 (deficit$ or disorder$ or dysfunc$)).tw.
22. (behav$ adj3 (dysfunc$ or disorder$)).tw.
23. (behav$ adj3 (dysfunc$ or disorder$)).tw.
24. (impulsiv$ or inattentiv$ or inattention$).tw.
25. disruptiv$.tw.
26. or/5-25
27. exp child/
28. adolescent/
29. (adoles$ or teen$ or youth$ or young people or young person$).tw.
30. (child$ or toddler$ or preschool$ or pre-school or schoolchild$ or schoolgirl$ or schoolboy$ or girl$ or boy$).tw.
31. Pediatrics/
32. p?ediatric$.tw.
33. or/27-32
34. 4 and 26 and 33
35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. randomi#ed.ab.
38. placebo$.ab.
39. drug therapy.fs.

40. randomly.ab.
41. trial.ab.
42. groups.ab.
43. or/35-42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 34 and 45

Lines 35 to 45 are the Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (Ovid version) (Lefebvre 2008)

Searching other resources

We will screen the reference lists of identified RCTs and review articles to identify additional publications. We will identify additional ongoing trials by searching Google Scholar.

Unpublished trials

We will request information on unpublished trials from authors of published studies and experts and information groups in the areas of ADHD and amphetamines.

Data collection and analysis

Selection of studies

Two review authors (SP and LS) will independently screen all the titles and abstracts retrieved from the search to identify those that appear to meet the inclusion criteria. We will classify the abstracts as either:

1. relevant (meeting all the prespecified inclusion criteria);
2. possible (meeting some, but not all, inclusion criteria); or
3. rejected (not relevant to the review, failing to meet any of the inclusion criteria).

Both review authors will then assess the full journal articles of all studies classified in categories 1 and 2 according to an inclusion/exclusion checklist. We will contact study authors up to three times if necessary to obtain information about unpublished studies or to obtain additional information to resolve questions about relevance of trials. We will resolve any disagreements by discussion, but where this is not possible, SV will adjudicate.

Data extraction and management

Two review authors (SP and LS) will independently extract data related to study methods, participant characteristics, and outcomes by using a predesigned data collection form. We will resolve any disagreements by discussion, and if need be, SV will adjudicate. SP will enter all relevant data into Review Manager 5.1 (RevMan 2011) and LS will double-check this.

Assessment of risk of bias in included studies

For each included study, two review authors (SP and LS) will independently assess the risk of bias in the seven domains explained below using the Cochrane 'Risk of bias' tool (Higgins 2011). We will resolve disagreements by discussion, but where this is not possible, SV will adjudicate.

We will assess the following sources of bias as being at low risk of bias, high risk of bias, or unclear (uncertain) risk of bias.

Random sequence generation

We will examine the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. Review authors' judgement: what is the risk of selection bias due to inadequate generation of a randomized sequence?

Allocation concealment

We will examine the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Review authors' judgement: what is the risk of selection bias due to inadequate concealment of allocations prior to assignment?

Blinding of participants and personnel

We will examine measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received and any information relating to whether the intended blinding was effective. Review authors' judgement: what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study?

Blinding of outcome assessment

We will examine measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received and any information relating to whether the intended blinding was effective. Review authors' judgement: what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessors?

Incomplete outcome data

We will examine data on attrition and exclusions and report the numbers involved (compared with total), reasons for attrition/exclusion where reported, or obtained from investigators, and any re-inclusions in analyses performed by review authors. Review authors' judgement: what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?

Selective reporting

We will examine attempts to assess the possibility of selective outcome reporting by investigators. We will attempt to retrieve the original protocols for each included study and compare the planned outcomes with the outcomes reported. Review authors' judgement: what is the risk of reporting bias due to selective outcome reporting?

Other sources of bias

We will make attempts to address sources of bias in other domains not covered by the tool. These include source of funding, conflicts of interest, and validity of outcome measures. Review authors' judgement: what is the risk of bias due to problems not covered elsewhere in the table?

Measures of treatment effect

Dichotomous outcome data

We plan to report risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous outcomes.

Continuous outcome data

For continuous outcomes, where the same rating scale has been used for all studies, we will calculate mean differences (MDs) and 95% CI; where different rating scales are used, we will calculate standardized mean differences (SMDs). Hedges' method will be used for calculating SMD with individual study weights calculated as the inverse of the variance. To ensure all scales are pointing in the same direction, we will multiply the mean values of one set by -1 (Higgins 2011). For the primary outcome, we will combine change scores and endpoint scores; however, we will give priority to change scores when both types of scores are available in the same study.

Unit of analysis issues

Cross-over trials

Our analysis will include both parallel and cross-over trials that will be combined in the same meta-analysis. For outcomes that use a MD, we will compute standard deviations (SDs) for the cross-over studies taking into account correlation. If correlation coefficients are not available, we will impute them from other studies or use 0.5 as a conservative estimate (Follman 1992). For outcomes using SMD, we will treat cross-over studies as if they were parallel and compute a pooled SD that does not take into account the cross-over. This will prevent overestimation of effect size.

In situations where carry-over is thought to be a problem, where no washout period is present, or when only data from the first period are available, we will analyze data from the first period only.

Studies with multiple comparisons

When more than two independent comparisons are available, for example, amphetamine versus placebo versus psychotherapy, we will not include the psychotherapy arm. In studies with multiple and correlated interventions, for example, lisdexamphetamine versus mixed amphetamine salts versus placebo, or 10 mg of amphetamine versus 20 mg of amphetamine versus placebo, we will combine the two experimental groups using the formulae described in Table 7.7.a of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Because we have planned a subgroup analysis for the different formulations of amphetamines, in order to avoid double-counts in the shared intervention groups (in this case placebo) for dichotomous outcomes, we will divide up both the number of events and number of participants. For continuous outcomes, we will divide up the total number of participants, while the means and SDs will be left unchanged (Higgins 2011).

Studies with multiple measures

When a single study provides multiple measures of the same outcome at the same point in time (for example, two measures used to assess ADHD severity), we will average the effects across the outcomes to arrive at a single effect for use in the meta-analysis.

Studies with multiple time points

In studies where results are presented for several periods of follow-up, we will analyze each outcome at each point in a separate meta-analysis with other comparable studies taking measures at a similar time frame post-randomization. Time frames will reflect short-term (up to six months), medium-term (between six and 12 months), and long-term (over 12 months) outcomes.

Dealing with missing data

We will contact authors of included studies up to three times to obtain missing data. If studies have not reported outcomes using intention-to-treat analysis, and the missing data are unattainable, we will perform an available case analysis for both dichotomous and continuous outcomes. If studies have not reported the SD, it will be calculated from P values, t values, CIs, or standard errors (as described in section 7.7.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). If this information is not reported or unattainable, the SD from the study with the highest SD for that outcome will be imputed. To assess the effect of missing data on the analysis, we will conduct a sensitivity

analysis for that outcome by showing our results with our imputed SD versus a lower imputed SD.

Assessment of heterogeneity

We will investigate clinical heterogeneity by performing subgroup analyses according to important clinical characteristics (presence of comorbid conditions; ADHD subtype), pharmacological characteristics (form of amphetamine used), study funding (pharmaceutically funded or not), and study design (cross-over versus parallel). We will explore statistical heterogeneity by examining the I^2 index (Higgins 2011), which is used to quantify the degree of heterogeneity in a meta-analysis. An $I^2 > 50\%$ in the primary analysis is indicative of statistical heterogeneity and we will determine whether to further explore clinical heterogeneity by performing subgroup analysis. We will calculate a pooled effect size for each subgroup.

Assessment of reporting biases

If we have identified a sufficient number of studies ($n \geq 10$) for inclusion, we will draw funnel plots in order to assess the possibility of publication bias. The degree of asymmetry will be examined using the Egger test (Egger 1997). Such a relationship could be due to publication bias, the relationship between trial size and effect size, or chance. If unpublished studies are included in the review, we will conduct a sensitivity analysis of published versus unpublished studies.

Data synthesis

Where we consider studies to be sufficiently homogenous in terms of participants (age, gender, etc), interventions (dosage, frequency, etc), and outcomes, we plan to synthesize results in a meta-analysis using the random-effects model. We will perform statistical analysis using The Cochrane Collaboration's Review Manager Software (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

If data permit, we will conduct subgroup analyses classifying the trials as follows.

1. Comorbidities: presence of comorbid ODD/CD or not.
2. Type of amphetamine: amphetamine, dextroamphetamine, lisdexamphetamine, or mixed amphetamine salts.
3. Type of drug release formulation: long-acting or immediate release.
4. Type of questionnaire used: completed by teacher, parent, clinician, investigator, or self.
5. Type of ADHD subtype: inattentive type, hyperactive-impulsive type, or combined type.

Sensitivity analysis

We will conduct sensitivity analyses classifying trials according to the following criteria.

1. Risk of bias assessment: each outcome meta-analysis will be restricted to those studies with a low risk of bias. A study is defined as having a low risk of bias if all domains of the risk of bias tool score a low risk of bias.
2. Study design: cross-over versus parallel RCTs.
3. Studies reporting the primary outcome as a change from baseline versus endpoint value.
4. Fixed-effect model of meta-analysis versus random-effects model.
5. Unpublished versus published studies.
6. Imputed SD versus lower imputed SD (in the event of missing data).

ACKNOWLEDGEMENTS

The authors wish to thank Margaret Anderson and Soleil Surrette for their assistance in developing and reviewing the search strategy.

REFERENCES

Additional references

Abidin 1997
Abidin RR. Parenting Stress Index: A measure of the parent-child system. In: Zalaquett CP, Wood RJ editor(s). *Evaluating Stress: A Book of Resources*. Lanham, MD, USA: Scarecrow Education, 1997:277–91.

AHRQ 1999
Agency for Health Care Policy and Research. Diagnosis of Attention-Deficit/Hyperactivity Disorder. Summary, Technical Review. http://www.ahrq.gov/clinic/epcsums/adhdsutr.htm (accessed 1 May 2012).

Anderson 1999
Anderson SW, Bechara A, Damasio H, Tranel D, Damasio AR. Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Natural Neuroscience* 1999;**2**:1032–7.

APA 1987
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. 3rd Edition. Washington, DC: American Psychiatric Association, 1987.

APA 2000
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. 4th Edition.

Washington, DC: American Psychiatric Association, 2000.

Arnsten 2006
Arnsten AFT. Stimulants: therapeutic actions in ADHD. *Neuropsychopharmacology* 2006;**31**:2376–83.

Biederman 1993
Biederman J, Faraon SV, Spencer T, Wilens T, Norma D, Lapey KA, et al.Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry* 1993;**150**(12):1792–8.

Buck 2002
Buck ML. Amphetamines in the treatment of attention-deficit/hyperactivity disorder. *Pediatric Pharmacotherapy* 2002;**8**(3):1–3.

Castells 2011
Castells X, Ramos-Quiroga JAntoni, Bosch R, Nogueira M, Casas M. Amphetamines for attention deficit hyperactivity disorder (ADHD) in adults. Cochrane Database of Systematic Reviews 2011, Issue 6. Art. No.: CD007813. DOI: 10.1002/14651858.CD007813.pub2.

Conners 1998
Conners CK, Sitarenios G, Parker JDA, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology* 1998;**26**(4):257–68.

Conners 1998a
Conners CK, Sitarenios G, Parker JDA, Epstein JN. Revision and restandardization of the Conners Teacher Rating Scale (CTRS-R): factor structure, reliability, and criterion validity. *Journal of Abnormal Child Psychology* 1998;**26**(4):279–91.

Edwards 1995
Edwards L, Salant V, Howard VF, Brougher J, McLaughlin TF. Effectiveness of self-management on attentional behavior and reading comprehension for children with attention deficit disorder. *Child and Family Behavior Therapy* 1995;**17**(2):1–17.

Egger 1997
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Follman 1992
Follman D, Elliott P, Suh I, Cutler J. Variance imputation for overviews of clinical trials with continuous response. *Journal of Clinical Epidemiology* 1992;**42**:769–73.

Higgins 2011
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. 5.1.0 (updated March 2011). Chichester: John Wiley & Sons, 2011. Available at www.cochrane–handbook.org.

Lefebvre 2008
Lefebvre C, Manheimer E, Glanville J. *Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions*. Wiley, 2008.

Mayes 2009
Mayes SD, Calhoun SL, Bixler EO, Vgontzas AN, Mahr F, Hillwig-Garcia J, et al.ADHD subtypes and comorbid anxiety, depression and oppositional-defiant disorder: differences in sleep problems. *Journal of Pediatric Psychology* 2009;**34**(33):328–37.

Moore 2011
Moore EA. Ritalin, Adderall and other treatments for ADHD. *The Amphetamine Debate: The Use of Adderall, Ritalin and Related Drugs for Behavior Modification, Neuroenhancement, and Anti-aging Purposes*. Jefferson, North Carolina: McFarland and Company, Inc, 2011: 80–107.

NIH 2000
National Institute of Health. National Institutes of Health consensus development conference statement: diagnosis and treatment of attention-deficit/hyperactivity disorder (ADHD). *Journal of the American Academy of Child and Adolescent Psychiatry* 2000;**39**(2):182–97.

NIMH 2009
National Institute for Mental Health. Attention Deficit Hyperactivity Disorder (ADHD). http://www.nimh.nih.gov/health/publications/attention-deficit-hyperactivity-disorder/complete-index.shtml (accessed 1 May 2012).

Polzancky 2007
Polanczyk G, Silva de Lima M, Horta BL, Biederman J, Rohde LA. Worldwide prevalence of ADHD. *American Journal of Psychiatry* 2007;**4**(164):942–8.

RevMan 2011
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Varni 1998
Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A. The Pediatric Quality of Life Inventory-32 (PedsQL-32): reliability and validity. *Cancer* 1998;**82**(6):1184–96.

Wigal 1999
Wigal T, Swanson JM, Regino R, Lerner MA, Soliman I, Steinoff K, et al.Stimulant medications for the treatment of ADHD: efficacy and limitations. *Mental Retardation and Development Disabilities Research Reviews* 1999;**5**(3): 215–24.

Zhang 2005
Zhang S, Faries DE, Vowles M, Michelson D. ADHD Rating Scale IV: psychometric properties from a multinational study as a clinician-administered instrument. *International Journal of Methods in Psychiatric Research* 2005; **14**(4):186–201.

* *Indicates the major publication for the study*

HISTORY

Protocol first published: Issue 7, 2012

CONTRIBUTIONS OF AUTHORS

SP and SV conceived this review.

SP will lead the design and ongoing co-ordination of this review with oversight from LS, LH, LU, BV, CJN, and SV.

SP developed the additional search strategies and will carry out the searches for this review.

SP and BV developed the analysis plan.

SP will retrieve the papers for this review.

SP and LS will screen the retrieved papers against the inclusion criteria for this review.

SP and LS will independently appraise the risk of bias in the papers for this review.

SP and LS will independently extract the data from the papers for this review.

SP will write to authors of included studies for additional information for this review.

SP will manage the data for this review including entering data into RevMan and analyzing the data under the guidance of BV.

SP will interpret the data for this review with input from all authors.

SP will write the review.

All authors will critically read and edit the review prior to submission.

DECLARATIONS OF INTEREST

- Salima Punja - none known.
- Larissa Shamseer - none known.
- Lisa Hartling - none known.
- Liana Urichuk - received salary support from the Addiction & Mental Health Program of Alberta Health Services-Edmonton Zone during the course of this review.
- Sunita Vohra - none known.
- Ben Vandermeer - none known.
- Catherine J Nikles - none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Alberta Innovates Health Solutions, Canada.

Salary support for Dr. Sunita Vohra